Quetiapine Extended-Release Versus Immediate-Release Formulation: A Positron Emission Tomography Study

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Objective: The pharmacokinetic and pharmacodynamic profile of the immediate-release (IR) formulation of quetiapine is characterized by a rapid peak in plasma level and striatal dopamine D_2 receptor occupancy, followed by a rapid decrease to baseline levels, necessitating the use of twice-daily dosing. An extended-release (XR) formulation of quetiapine is currently being developed to achieve similar efficacy using a once-daily dosing regimen. We compared the central D_2 receptor binding between the IR and XR formulations.

Method: In this open-label, crossover positron emission tomography study using [^{11}C]-raclopride, we compared the central D_2 receptor binding potential at expected peak and trough plasma levels using equivalent daily doses of the IR and XR formulations (300, 600, and 800 mg/day) in 12 subjects. Data were collected from April 2002 to May 2003.

Results: The mean plasma level of quetiapine at trough was significantly lower than that at peak for all dose groups of both formulations except for IR 300 and 800 mg (all p values < .05), while the mean plasma level did not differ significantly between formulations at trough and peak. The mean occupancy at peak was significantly higher than that at trough for all dose groups other than IR 800 mg/day (all p values < .05) and did not differ significantly between formulations at trough and peak.

Conclusion: Once-daily dosing of the XR formulation gives peak and trough plasma levels and central D_2 receptor occupancy comparable to twice-daily dosing of the IR formulation. These data should be considered while determining equivalent doses, as well as switching strategies.

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Positron emission tomography (PET) studies have shown that, for most antipsychotics, the likelihood of clinical response is higher when at least 60% of central D_2 receptors are occupied by the drug, while extrapyramidal side effects (EPS) tend to occur when the D_2 receptor occupancy exceeds 80%.[1–3] Quetiapine, like clozapine, is an effective antipsychotic at lower D_2 receptor occupancy, which may account for its very low risk of EPS and prolactin elevation.[4,5] At daily doses of 450 to 600 mg, its D_2 occupancy peaks within 2 to 3 hours of its administration (45%–60%) and then declines rapidly to less than 30% 12 hours after the last dose, which is consistent with its known plasma pharmacokinetics.[5,6] Its rapid pharmacokinetics necessitates twice-daily dosing, which could lower adherence to the treatment.[7,8] An extended-release (XR) formulation of quetiapine fumarate is currently being developed with the goal of achieving similar efficacy

using a once-daily dosing regimen.[9,10] Compared to the immediate-release (IR) formulation,[11] the XR formulation shows a more gradual rise in plasma level (t_{max} = 6 hours) and a slower decline over a 24-hour period ($t_{1/2}$ = 7 hours) (data on file, AstraZeneca Pharmaceuticals, Wilmington, Del.). Pharmacokinetic studies have supported the bioequivalence of once-daily doses of 300 mg XR formulation with twice-daily doses of 150 mg IR formulation (steady-state area under the curve = 0–24, IR = 5882 ng.h/mL, XR = 6147 ng.h/mL) (data on file, AstraZeneca Pharmaceuticals, Wilmington, Del.). Mean C_{max} of the XR formulation (495.3 ng/mL) was slightly lower than that of the IR formulation (568.1 ng/mL), whereas there was minimal difference between formulations with respect to C_{min} (95.3 ng/mL and 96.5 ng/mL for the IR and XR formulations, respectively).

However, plasma levels do not robustly predict clinical response for antipsychotic drugs,[12] and this fact may be partly related to dissociation between plasma kinetics and central (receptor-occupancy) kinetics.[13] Thus, insofar as predicting the outcome of the quetiapine XR formulation, it would be valuable to know whether once-daily dosing of a given dose of the XR formulation results in central-receptor occupancy similar to twice-daily dosing of the equivalent dose of the IR formulation. We therefore conducted a crossover PET study designed to compare the central D_2 receptor occupancy at expected peak and trough plasma levels in patients treated with quetiapine IR formulation switched to equivalent once-daily doses of the XR formulation.

METHOD

This study was conducted at the University of Toronto between April 2002 and May 2003. The study was approved by the Human Subjects Review Committee of the University of Toronto, and subjects provided written informed consent after receiving detailed information about the protocol. Male and female patients were included if they were between the ages of 18 and 50; met DSM-IV criteria for either schizophrenia, schizoaffective disorder, schizophreniform disorder, or delusional disorder; had received continuous treatment with quetiapine IR as monotherapy for at least 2 weeks at the time of study enrollment; and were capable of providing informed consent. Subjects were excluded if they had a history of treatment with a depot antipsychotic within 12 months, a history of substance abuse within 3 months of the study, a positive urine drug screen at screening, or a history of serious neurologic or general medical conditions.

The study design involved an open-label, fixed-dose, crossover PET imaging study using [^{11}C]-raclopride to study D_2 receptor occupancy of equivalent doses of quetiapine IR versus XR formulations. On enrollment, subjects were assigned to 1 of 3 dose groups—300, 600, or 800 mg/day—on the basis of the subjects' quetiapine dose at the time of enrollment. Dose was then titrated to the assigned dose using the IR formulation dosed on a b.i.d. basis at 8 a.m. and 8 p.m. Four days following completion of titration, subjects underwent 2 [^{11}C]-raclopride PET scans. The first scan was completed at 9:00 a.m. (representing expected *trough* plasma levels), followed by administration of the next dose of IR formulation at 10:15 a.m. and a second [^{11}C]-raclopride PET scan 1 hour postadministration (representing expected *peak* plasma levels). On the following day, subjects were switched to the equivalent dose of the XR formulation taken once a day at 9 a.m. (commencing the morning following PET scans 1 & 2). On day 4 of this XR treatment, subjects underwent 2 final [^{11}C]-raclopride scans: The first scan was completed at 9 a.m. (representing trough plasma levels), followed by administration of the XR formulation dose at 10:15 a.m. and a final [^{11}C]-raclopride scan 5 hours postadministration (representing peak plasma levels). While clinical outcome was not the primary objective of the study, the following clinical rating scales were completed at baseline and at the time of IR and XR PET scans: the Clinical Global Impressions-Severity of Illness subscale (CGI-S),[14] the Simpson-Angus Scale (SAS),[15] the Barnes Akathisia Scale (BAS),[16] and the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale.[17]

The [^{11}C]-raclopride PET scans for D_2 receptor occupancy were obtained immediately following injection of 10 mCi of high specific-activity [^{11}C]-raclopride (> 300 Ci/mmol) using a bolus plus infusion protocol,[18–21] with 59% injected as a bolus over 1 minute and the rest injected via intravenous infusion over 74 minutes. Following a brief transmission scan for attenuation correction of the emission scans, a continuous series of emission scans was obtained every minute for the first 15 minutes and then every 5 minutes until the end of the scan at 75 minutes. PET scanning was conducted using a brain-only GEMS PC2048-Plus PET camera (General Electric Medical Systems, Milwaukee, Wis.) that produced 6.5-mm-thick slices with a resolution of about 5 mm in air. Patients were scanned lying down and with fixation of the head achieved using a thermoplastic face mask (Tru-Scan Imaging, Annapolis, Md.), allowing for repositioning between procedures.

To permit accurate delineation of the brain regions for data analysis, each patient had a magnetic resonance imaging (MRI) scan done using a GE-Signal 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, Wis.). The image was acquired using a conventional T1 localizing scan and fast spin echo sequence (both PD/T2 and T1) with 3-mm slice thickness. The MRI scan of each patient was coregistered to his or her PET scan using RView8 software.[22] The regions of interest (ROIs) used in the analysis of D_2 occupancy were the caudate/putamen,

with the cerebellum used as a reference region. The ROI analysis was completed by a single rater (I.V.) using Alice 3.1 (Perceptive Systems, Boulder, Co.). This software allows the rater to draw the ROI on an MRI image that was coregistered to summed PET images (representing averaged images of the dynamic time series). The ROIs were then transferred to the dynamic PET images using the same software, and a time-activity curve was generated and used in the analysis.

D_2 receptor binding potential (BP) was estimated using previously described methods,[23,24] using the mean of the striatum/cerebellum ratio obtained between 30 to 75 minutes of scanning as an estimate of the equilibrium BP. This timing was chosen on the basis of previous studies showing a very high correlation of the BP derived from the ratio method with analytically derived estimates of D_2 receptor BP ($r > 0.95$).[25] It is highly reliable, with a scan-rescan standard deviation of 6%, and has been standardized in our lab with a high intrarater and interrater reliability (intraclass correlation coefficients: $r > 0.95$).[26] Since dopamine D_2 receptor BP, which is proportional to the ratio of B_{max} (the total number of receptors) to k_d (the affinity of the drug for the receptor),[23] declines proportionately with age,[27] we calculated the occupancy (%) of the drug at D_2 receptors using age-corrected BP measures obtained from a previously collected dataset of 21 antipsychotic-free healthy subjects. The data from these subjects were reanalyzed by the same rater to ensure within-study consistency. Receptor occupancy for a given dose was calculated as the percentage reduction of receptor BP with drug treatment compared to baseline ($100 \times \{1 - [BP_{drug\ scan}/BP_{baseline}]\}$). The absence of the patients' own baseline values introduces a potential error: this error, as calculated on the basis of variance in the data from antipsychotic-naive patients, is expected to vary from 0% to 9% for patients with 50% occupancy and from 0% to 4% for patients with 80% occupancy; however, since the major comparison in this study was a within-subject occupancy on 2 formulations, this error is controlled for.

Venous blood was collected for quetiapine and prolactin plasma levels at the time of the respective PET scans. The levels of quetiapine were examined in heparinized plasma using high-performance liquid chromatography at the bioanalysis department at AstraZeneca U.S.A., with a limit of quantitation of 2.5 ng/mL. Prolactin levels were determined locally using chemiluminometric immunoassay with a minimum detectable limit of 1 μg/L.

Statistical Analyses

Statistical analyses were carried out using SPSS (SPSS Inc., Chicago, Ill.). The Pearson linear correlation was employed to examine the relationship between the primary variables of interest. Analysis of covariance with plasma quetiapine level as a covariate was performed to compare BP between both formulations. The Student t test and paired t test were used to examine differences in continuous and ratio variables, and the Wilcoxon signed rank test, the Friedman test, and the Fisher exact test were used to examine changes in clinical variables. A 2-tailed p value of < .05 was considered statistically significant.

Table 1. Plasma Quetiapine Levels at the Time of the PET Scans[a]

Dose, mg/d	Quetiapine Plasma Level, Mean ± SE, ng/mL			
	IR_{Trough}	IR_{Peak}	XR_{Trough}	XR_{Peak}
300	37.0 ± 1.8	351.3 ± 102.0	55.5 ± 9.3	427.3 ± 114.8**
600	121.0 ± 27.0	807.8 ± 166.5*	172.5 ± 21.0	543.8 ± 53.3**
800	111.0 ± 47.2	308.8 ± 119.4	120.8 ± 93.3	641.3 ± 191.6**

[a]The mean plasma level at trough was significantly lower than that at peak for all dose groups of both formulations except for IR 300 mg and 800 mg. There were no significant differences between formulations at trough and peak for all dose groups.
*$p < .05$ vs. IR_{Trough}.
**$p < .05$ vs. XR_{Trough}.
Abbreviations: IR = immediate-release, PET = positron emission tomography, XR = extended-release.

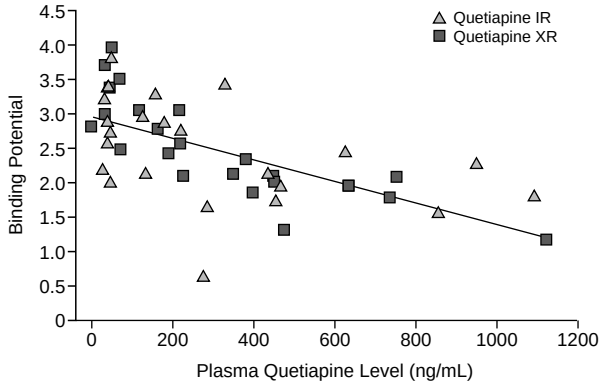
RESULTS

Fourteen subjects completed the informed consent process, and 2 subjects were discontinued due to failure in screening laboratory testing (abnormal baseline laboratory values and abnormal findings in electrocardiogram). The remaining 12 subjects (male = 10; mean ± SD age = 32 ± 8 years) completed the study, with 4 subjects per dose group. The subjects' DSM-IV diagnoses were schizophrenia (N = 11) and schizoaffective disorder (N = 1). Four of the 12 subjects required a small increase in dose from baseline prestudy dose to reach the target doses required in the study protocol (from 400 to 600 mg, N = 2; from 475 to 600 mg, N = 1; from 700 to 800 mg, N = 1), while only 1 subject required a small decrease in dose from the prestudy dose (from 850 to 800 mg).

The mean plasma levels in the 3 dose groups at the time of the 4 PET scans is represented in Table 1. The mean plasma level of quetiapine at trough was significantly lower than that at peak for all dose groups of both formulations other than IR 300 mg/day and IR 800 mg/day. However, the mean plasma level did not differ significantly between formulations at trough and peak for all dose groups.

Plasma quetiapine level was negatively correlated with BP ($r = –0.63$, $p < .001$) (Figure 1), with no group difference between both formulations ($p = .89$). Consistent with our plasma pharmacokinetic results described above, the mean BP at peak was significantly lower than that at trough for all dose groups of both formulations except IR 800 mg/day. The mean D_2 receptor occupancy was significantly higher at peak than at trough for both IR and XR formulations for all dose groups except IR 800 mg/day group (Table 2). However, neither

Figure 1. Relationship Between Binding Potential and Plasma Quetiapine Level[a]



[a]Plasma quetiapine level was negatively correlated with binding potential (r = –0.63, p < .001), with no group difference between the IR and XR formulations (p = .89).
Abbreviations: IR = immediate-release, XR = extended-release.

Table 2. D_2 Receptor Occupancy at the Time of the PET Scans[a]

Dose, mg/d	D_2 Receptor Occupancy, Mean ± SE			
	IR_{Trough}	IR_{Peak}	XR_{Trough}	XR_{Peak}
300	–4.5 ± 8.7	37.3 ± 2.4*	–5.5 ± 12.7	26.5 ± 8.5**
600	8.0 ± 12.2	29.0 ± 14.3*	12.4 ± 6.8	38.5 ± 2.6**
800	24.0 ± 8.8	47.0 ± 14.3	17.9 ± 15.2	56.1 ± 6.7**

[a]The mean D_2 receptor occupancy showed a significantly higher number at peak than at trough for all dose groups of both formulations except IR 800 mg. There were no significant differences between formulations at trough and peak for all dose groups.
*p < .05 vs. IR_{Trough}.
**p < .05 vs. XR_{Trough}.
Abbreviations: IR = immediate-release, PET = positron emission tomography, XR = extended-release.

the BP nor D_2 receptor occupancy differed significantly between formulations at trough and peak for all dose groups.

Due to the small number of subjects in this study, results relating to clinical outcome will be reported for descriptive purposes only. A significant change was found in the CGI-S scores (χ^2 = 9.415, df = 2, p = .009), and the median severity score on the CGI-S scale increased from 2 on the prestudy dose at visit 2 ("borderline mentally ill") to 4 at the time of the IR PET scans ("moderately mentally ill") (z = 2.56, p = .011) and remained unchanged at the time of the XR PET scans (z = 0.48, p = .66). We found no significant change in scores on the BAS (χ^2 = 1.00, df = 2, p = .607) and SAS (χ^2 = 4.16, df = 2, p = .125) during the study. The total number of newly emergent adverse events (AEs) or worsening of preexistent adverse events (including sedation and sleep disturbance) during the study was higher for the IR formulation (AEs = 41) than for the XR formulation (AEs = 20). Among AEs rated by the UKU side effect scale, only orthostatic dizziness showed a significant difference in the incidence between formulations (33.3% and 0.0% for the IR and XR formulations, respectively, p = .047).

Three subjects showed an increase in prolactin level above the reference range (male = 2–18 μg/L, female = 3–29 μg/L), one 25-year-old woman treated with 800 mg/day XR at peak state (prolactin = 45.9 μg/L) and 2 men (30 and 33 years old) treated with 600 mg/day IR and 800 mg/day XR, respectively, both at peak plasma levels (prolactin = 23 and 27 μg/L, respectively). Plasma quetiapine levels at the time of the PET scans showed a significant positive correlation with plasma prolactin levels (r = 0.51, p < .001).

DISCUSSION

To our knowledge, this is the first reported comparison of central D_2 receptor binding of the IR and XR formulations in patients with schizophrenia spectrum disorders. We found that once-daily dosing of the XR formulation resulted in peak and trough plasma levels similar to the IR formulation, consistent with their respective pharmacokinetics (data on file, AstraZeneca Pharmaceuticals, Wilmington, Del.). The resulting striatal D_2 receptor binding of the drug, a surrogate pharmacodynamic marker for clinical efficacy, is similar for both formulations at peak and trough plasma levels. This outcome predicts similar clinical efficacy, which is supported by recent clinical trials comparing clinical efficacy between those 2 formulations.[9,10] For the XR formulation, we also found the expected dose effect on D_2 receptor occupancy, calculated using age-corrected measures of BP at both trough and peak (Table 2). This dose-occupancy relationship was only noted at trough for the IR formulation.

Previous PET studies have suggested that, for most antipsychotics, with the possible exception of clozapine, consistent clinical antipsychotic effects are observed at striatal D_2 occupancy equal to or greater than 60%. In this study, the D_2 mean ± SE occupancy at peak plasma levels for 800 mg of the IR and XR formulations was 47.0% ± 14.3% and 56.1% ± 6.7%, respectively, which is below the threshold associated with antipsychotic response in all other antipsychotic drugs, excluding clozapine.[3,25,28] Quetiapine may also be an exception to this rule, though there is reason to question this proposition. A significant correlation was previously observed between plasma quetiapine levels and clinical improvements in schizophrenia patients treated with 50 to 1200 mg/day,[29] and a number of case series reporting on the clinical efficacy and tolerability of quetiapine at doses higher than 800 mg/day have suggested possible therapeutic benefits of such a regimen in selected patients.[30–32] The availability of an XR formulation with a better tolerability profile may

provide an opportunity to reexamine this purported lower occupancy threshold for quetiapine.

The clinical significance of achieving a single peak in plasma level with the XR formulation compared to twice-daily dosing with the IR formulation is not known, especially since we observed no significant difference in mean plasma levels between formulations at trough and peak. Our observation of a higher number of AEs for the IR formulation compared to the XR formulation needs to be followed up in larger clinical studies. If confirmed, it is possible that rapid shifts in plasma levels and/or dopamine D_2 receptor occupancy may be contributory to this difference for the IR formulation.

This study was designed with the primary objective of comparing central occupancy of D_2 receptors by equivalent doses of the IR and XR formulations. Hence, the interpretation of the clinical outcome measure needs to be done in light of the small numbers, unblinded design, very brief duration, and absence of placebo control. For example, the small increase in the median CGI-S score was seen after target doses of both IR and XR were reached as compared to the baseline, particularly since, of those 5 subjects who needed a very small dose adjustment in the first week to reach the target dose, only 1 required a very small decrease in daily dosing. However, despite the limitations of the current study in terms of assessing efficacy, recent double-blind, randomized controlled trials have clearly supported the therapeutic efficacy of the XR formulation.[9,10] It is also of note that IR_{peak} plasma levels were not proportional to given doses, and wide interindividual differences were reflected in large standard errors in plasma quetiapine levels. These findings may be due to individual differences in pharmacokinetics, particularly at expected peak plasma levels for antipsychotics with a short half-life, including quetiapine. T_{max} was not individually measured in this study but, on the basis of past pharmacokinetic data, was expected to be uniform, which would be expected to induce errors. Similarly, these wide interindividual differences were observed also in D_2 occupancy, which may be derived from the wide individual variations in pharmacokinetics and a lack of baseline BP. Finally, some nonsignificant differences observed between both formulations in this study may be derived from a type II error due to the small sample size.

CONCLUSION

We compared the striatal D_2 occupancy of IR and XR formulations of quetiapine at expected peak and trough plasma levels and found that once-daily dosing of the XR formulation resulted in central D_2 receptor occupancy comparable to twice-daily dosing of the IR formulation. These data should be considered while determining equivalent doses as well as switching strategies.

Drug names: clozapine (FazaClo, Clozaril, and others), quetiapine (Seroquel).

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